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Brain Structural Covariance Network in Asperger Syndrome Differs From Those in Autism Spectrum Disorder and Healthy Controls

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ABSTRACT

Introduction: Autism is a heterogeneous neurodevelopmental disorder associated with social, cognitive and behavioral impairments. These impairments are often reported along with alteration of the brain structure such as abnormal changes in the grey matter (GM) density. However, it is not yet clear whether these changes could be used to differentiate various subtypes of autism spectrum disorder (ASD).

Method: We compared the regional changes of GM density in ASD, Asperger's Syndrome (AS) individuals and a group of healthy controls (HC). In addition to regional changes itself, the amount of GM density changes in one region as compared to other brain regions was also calculated. We hypothesized that this structural covariance network could differentiate the AS individuals from the ASD and HC groups. Therefore, statistical analysis was performed on the MRI data of 70 male subjects including 26 ASD (age=14-50, IQ=92-132), 16 AS (age=7-58, IQ=93-133) and 28 HC (age=9-39, IQ=95-144).

Result: The one-way ANOVA on the GM density of 116 anatomically separated regions showed significant differences among the groups. The pattern of structural covariance network indicated that covariation of GM density between the brain regions is altered in ASD.

Conclusion: This changed structural covariance could be considered as a reason for less efficient segregation and integration of information in the brain that could lead to cognitive dysfunctions in autism. We hope these findings could improve our understanding about the pathobiology of autism and may pave the way towards a more effective intervention paradigm.

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Highlights

- ASD group showed increased GM at precentral gyrus and vermis as compare to HC.
- AS group showed increased and decreased GM at several parts of brain as compare to HC.
- ASD group showed increased structural covariance at frontal and decreased structural covariance at temporal as compare to HC.
- AS and ASD groups showed similar pattern of connectivity. While, the connectivity between brain regions were more stronger in AS group.
- Increased brain alteration in AS group as compare to ASD, may imply as existence of compensatory mechanism for better cognitive performance

Plain Language Summary

In this study, alteration of regional grey matter density in autistic and Asperger individuals as compared to a group of healthy controls was investigated. In addition, covariation of regional GM density in pairs of 116 anatomically separated regions was also calculated and the group differences were identified. Our analysis revealed significant changes in the regional GM density, as well as the pattern of structural covariance between the 3 above-mentioned groups. The ASD group showed higher GM density at the precentral gyrus and vermis as compare to HC. The AS group showed decreased GM density at limbic and interior–temporal, but increased GM at cingulate and medial frontal. Structural covariance analysis showed increased and decreased inter-hemispheric correlation at frontal and temporal accordingly. Increased intra-hemispheric correlation at temporal, parietal, insula, posterior fossa regions were also observed in ASD. Similar pattern but with more severe degree was observed in AS individuals versus HCs. Increased GM and structural covariance in AS group may imply as existence of compensatory mechanism to lead better cognitive performance in this group as compare to ASD group.

1. Introduction

Autism spectrum disorder (ASD) as a neurodevelopmental disorder is characterized by deficits in communication and reciprocal social interaction and restricted, repetitive, or stereotyped patterns of behavior (McAlonan et al., 2008). Whereas Asperger syndrome (AS) is a distinct type of ASD that shares most of the clinical features of classical ASD but has significant language delay (Gilchrist et al., 2001). There are also behavioral differences between ASD and AS, like performance intelligence quotient (IQ) (Szatmari, et al., 1995), motor performance (Volkmar, et al., 1998), emotion perception (Mazefsky & Oswald, 2007), empathy (Montgomery et al., 2016), sensory experience (Bogdashina, 2016), executive function, the severity of repetitive behavior (Ozonoff, et al., 2000), and development of the theory of mind (Montgomery et al., 2016). Differences in cognitive, language, school functioning, and comorbidity were also found between AS and ASD (de Giambattista et al., 2019; Bi, et al., 2018). Neuroimaging studies have linked these traits to structural abnormalities in the brain. For example, Recent studies have reported brain structural abnormalities in the frontal, temporal, parietal, and striothalamic networks in ASD (Ecker et al., 2017). Increased gray matter (GM) in angular gyrus (Liu et al., 2017) and regions, including default mode network (Uddin et al., 2011), as well as less GM in the right paracingulate sulcus, left inferior frontal gyrus (Abell et al., 1999) and cerebellum (D'Mello, et al., 2016) has also been reported in ASD. GM volume reduction in the striatum and amygdala/hippocampus has been frequently reported in ASD (Van Rooij et al., 2018). One of the recent meta-analyses of voxel-based morphometry studies in over 900 ASD patients, found GM volume decrease in the medial prefrontal cortex (mPFC) and posterior insula and an increase in left anterior temporal, right inferior temporoparietal, left dorsolateral prefrontal (DLPFC), and precentral cortices (Carlisi et al., 2017). Other studies considered the relationship between white matter (WM) and GM. For example, Cauda found positive concordance of WM and GM in the left hemisphere and negative concordance in the right hemisphere in ASD (Cauda et al., 2014).

Studies on Asperger syndrome have also shown GM abnormality in the cingulate gyrus (Kwon, et al., 2004), cerebellum, putamen, precuneus, and amygdala (Kevin & McAlonan, 2011). Although GM abnormalities have been reported in ASD and AS individuals, much less is known about the differentiation between them (Khosrowabadi, et al., 2015; Sadeghi et al., 2017b). Faridi and Khosrowabadi reviewed some of the important factors, including the effect of age, gender, and IQ on Asperger syndrome. In their study, the effect of each factor on behavioral, chemical, and brain structural changes is discussed (Faridi & Khosrowabadi, 2017).

The grey matter changes are region-specific (Stacey et al., 2017; Kobayashi et al., 2020). Therefore, covariation of regional changes could introduce another measure known as structural covariance (SC) (Mechelli, et al.e, 2005). The SC is mainly based on the phenomenon that inter-individual differences in a brain region often covariate with other brain regions that simultaneously fluctuate (Evans, 2013). Pathological structural covariance has been demonstrated in cases of ASD. For example, large-scale disruption of the frontotemporal SC network in an individual with ASD which play a central role in language and communication has been demonstrated (Sharda, et al., 2016). Other studies have reported a disrupted structural correlation between brain regions that are responsible for social functions in autism (McAlonan et al., 2005; Dziobek, et al., 2010). Reduced local and increased long-ranged functional connectivity of the thalamus (Tomasi & Volkow, 2019), insula (Guo et al., 2019), and amygdala (Guo et al., 2016) have also been identified. Moreover, decreased inter-hemispheric and enhanced intra-hemispheric structural covariation have been shown in recent studies (Duan et al., 2020). One structural covariance study of sensory networks demonstrated decreased structural covariation between sensory-related cortical structures, especially between the left and right cerebral hemispheres, but increased structural covariance of the structure in the right cerebral hemisphere in individuals with ASD (Cardon, et al., 2017).

However, it needs to be investigated whether the SC varies between ASD and AS. So, this study hypothesized that structural grey matter changes vary in ASD, AS, and healthy control (HC) groups. To test the hypothesis, grey matter changes were estimated from MRI scans in ASD, AS and HC groups. After the calculation of regional GM density, the covariation of GM changes between pairs of brain regions was calculated. Subsequently, statistical analysis was performed to highlight the structural covariance changes among the groups.

2. Materials and Methods

Study participants

A total of 42 subjects with a DSM-IV-TR diagnosis of autism, including 16 AS (Mean±SD age=24.31±15.810 years, IQ=111.31±11.241) and 26 ASD (Mean±SD age=24.67±8.347 years, IQ=110.26±12.09) with 28 HC (mean ± SD age=22.13± 8.579 years, IQ=115.92±12.66) participants were studied. All subjects were male and right-hand dominant. ASD and HC subjects were selected from the dataset of USM (University of Utah School of Medicine) and AS subjects were selected from the dataset of LMU (Ludwig Maximilian University Munich). A summary of the demographic characteristics of each group is provided in Table 1. Informed written consent was obtained for all participants and the procedure was approved by the human investigation Review Board at the University of Utah School of Medicine and Ludwig Maximilian University Munich. Estimates of full IQ above 92 and absence of other chronic medical conditions were required for all subjects. Additionally, these measures are all correlated with the Wechsler Abbreviated Scale of Intelligence.

Data acquisition

All participants underwent a T1-weighted high-resolution MRI scanning using a 3 Tesla Siemens scanner system (SIMENS MAGNETOM TrioTim syngo MR B17) with the following protocol: T1=900 ms; Flip angle=9º; TR=2300 ms; TE=2.91 ms; Slices=160; Orientation=Sagittal; Slice thickness=1.20 mm; and voxel size=1.0×1.0×1.2 mm. All imaging data used are publicly available at http://fcon_1000.projects.nitrc.org/indi/abide/abide_I.html.

Magnetic resonance imaging (MRI) data processing

Standard preprocessing was performed on MRI data using the FMRIB software library (FSL: http://www.fmrib.ox.ac.uk/fsl) (Jenkinson, et al., 2012) and analysis of functional neuroimaging (AFNI: http://afni.nimh.nih.gov/afni) (Cox, 1996). All participants' structural images were checked for scanner and individual-based motion artifacts. Then, images were deobliqued before reorientation to FSL-friendly space. Subsequently, individual images were affine registered to Montreal Neurological Institute and Hospital (MNI) space and then corrected for bias-field in homogeneities. Next, MRI images were segmented into different tissue types through the FSL FMRIB's Automated Segmentation Tool (FAST) by partial volume modeling. All images were then spatially

normalized. Afterward, the MRI grey matter segment of each subject was parcellated into 116 regions of interest (ROI) using MNI-normalized automated anatomical labelling (AAL) atlas. Therefore, 116 ROIs were acquired for each participant that present the average GM density at the specified region of the brain. Finally, a region-wise statistical analysis was performed across different groups (Figure 1).

Statistical analysis

Differential pattern of brain anatomical changes in AS, ASD, and HC groups

In this stage, the grey matter density of each ROI for each group individually was statistically compared to the same ROI in another group using a 2-sample t test. The comparison was performed for each pair of groups separately. Since the comparisons were performed for each ROI separately, a correction was also performed for multiple comparison effects. Statistical analyses were performed using the statistical toolbox of MATLAB 2013a software. A significance level of $P<0.005$, corrected for false discovery rate (FDR), was considered for presenting the results.

Construction of structural connectivity network (SCN)

The covariance of GM density between the brain regions was calculated for each group separately. GM density of all 116 anatomical regions for each individual was used to construct the structural connectivity network (SCN). For each group, an association matrix (N×116, N=number of samples) was implied to generate the SCN (R=116×116) by computing the Pearson correlation (ri,j) between the vector of GM density in region i and region j across participants. The extracted SCN of the AS group was then statistically compared to the SCNs of ASD and HC groups.

Comparing between SCNs of AS, ASD, and HC groups

The SCNs were extracted based on similarities of the regional GM density. The correlation coefficients of each group were compared to another using the 'cocor' software package (version 1.1, Fisher's Z test 1925) written in the R 3.2.5 programming language. In this research, the correlation coefficients (r, p considering the sample size) of each group was calculated using MATLAB Software. Then, statistical analysis was conducted between each pair of groups in R statistical software by transferring r values to z values using Fisher's z test and $P<0.005$ were considered significant results.

3. Results

As presented in Table 1, there were no significant differences between the groups in age and IQ scores. The regional grey matter density and structural covariance network in AS, ASD, and HC groups was computed based on the subjects' MRI data. Subsequently, differences between the groups were calculated by statistical comparison between their measures. Significant differences in the regional GM density between the groups ($P<0.05$, false discovery rate [FDR] corrected) are presented in Tables 2 to 4, and Figure 2. In addition, structural covariance networks of AS, ASD, and HC groups are presented in Figure 3 and their significant differences are shown in Figure 4. Details of results presented in Figure 3 are presented in supplementary material in Tables S1 to S3.

Differential pattern of grey matter density in AS, ASD, and HC groups

ASD group compared to HCs showed an increase in GM density at the precentral and vermis regions (Table 2, Figure 2A). Moreover, AS groups compared to HCs showed raised GM density at the frontal medial orbital and anterior cingulum bilaterally and superior orbitofrontal, middle orbitofrontal, and inferior triangle frontal at the right hemisphere. While decreased GM density was found in the hippocampus, parahippocampal, cuneus, fusiform, caudate, putamen, pallidum, thalamus, heschle, cerebellum crus 1, cerebellum 3, 4-5, 6, 7b, 8, 9 bilaterally, amygdala and cerebellum crus 2 at the right side, olfactory, calcarine, lingual, middle occipital, postcentral at the left side and vermis 3, 4-5, 7, 8, 9 (Table 3, Figure 2B). In addition, AS group compared to the ASD group showed increased GM density at the medial orbitofrontal and anterior cingulum bilaterally, and frontal superior orbital and frontal inferior triangle on the right hemisphere. In contrast, decreased GM density was also found at the olfactory, hippocampus, para-hippocampal, amygdala, cuneus, fusiform, caudate, putamen, pallidum, thalamus, heschle, cerebellum crus 1, cerebellum 3, 4-5, 6, 8, 9 bilaterally, and insula, calcarine, lingual, middle occipital, postcentral at the left side, and cerebellum crus 2, cerebellum 7b at the right side, as well as vermis 3, 4-5, 6,7, 8, 9 (Table 4, Figure 2C). In Figure 2, increased GM density is shown in red, and decreased GM density is in blue.

Table 1. Demographics of the subjects

Study Groups	Age (y)			Full IQ		
	Mean±SD		Range	Mean±SD		Range
Asperger syndrome (AS), n=16	24.31±15.810		7-58	111.31±11.241		93-133
Autism spectrum disorder (ASD), n=26	24.67±8.347		14-50	110.26±12.091		92-132
Healthy control (HC), n=28	22.13±8.579		9-39	115.92±12.669		95-144
Statistical comparison Two-sample t-test	AS vs HC	ASD vs HC	AS vs ASD	AS vs HC	ASD vs HC	AS vs ASD
t	0.595	1.103	-0.098	-1.209	-1.676	0.278
P	0.554	0.274	0.922	0.233	0.099	0.781

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Structural covariance network in AS, ASD, and HC

The structural covariance network based on regional GM density in each group is presented in Figure 3 and their statistical differences are shown in Figure 4. In Figure 3, the red color denotes a positive correlation between regions, while the blue color indicates a negative association. Interestingly, all 3 groups mainly showed a significant positive association between the regional GM densities (P<0.05, FEW corrected).

Differential pattern of SCNs in AS, ASD, and HC groups

The Asperger syndrome group as compared to ASD had increased inter-regional correlation at the posterior fossa and excessive intra-regional correlation at frontotemporal and frontoparietal associations. Nevertheless, the correlation between GM density at the posterior fossa and other regions (frontal, temporal, parietal, occipital, insula) was decreased (Figure 4A). Similar pattern but with the more severe degree was observed in AS individuals versus the HC group (Figure 4B). Moreover, compared to HC, ASD showed an increased inter-hemispheric correlation of GM density at posterior fossa and frontal regions. In addition, increased intra-hemispheric correlation between GM density of the temporal region and parietal, insula, and posterior fossa regions were observed. However, inter-hemispheric associations between GM density at the temporal region and other brain regions were decreased (Figure 4C).

4. Discussion

In this study, the alteration of regional grey matter density in autistic and Asperger individuals compared to healthy controls was investigated. In addition, covariation of regional GM density in pairs of 116 anatomically separated regions was also calculated and the group differences were identified. Our analysis revealed significant changes in the regional GM density, as well as the pattern of structural covariance between the 3 above-mentioned groups.

The ASD group compared to the HC group presented higher GM density at the precentral gyrus and vermis. This result is consistent with previous MRI studies (Hyde, et al., 2010; Courchesne, et al.n, 1988). The precentral gyrus is believed to be involved in motor control, and the vermis has crucial importance in emotion regulation and emotion processing paradigms, as well as the oculomotor control that all are disrupted in the ASD group (Kato & Izumiyama, 2015; Beauregard et al., 1998; Laidi et al., 2017). The increased GM density at the precentral gyrus in the ASD group might be due to excessive gyrification that has been reported in sev-

Table 2. Regional changes of the grey matter density in autistic individuals as compared to healthy controls

Brain Region	Hemisphere	t	P	MNI Coordinates (x, y, z)
Precentral gyrus	Right	2.019	0.049	41, -8, 52
Vermis-8	---	2.253	0.028	2, -64, -34

MNI: Montreal neurological institute, and hospital.

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Table 3. Regional changes of the grey matter density in ssperger syndrome compared to healthy controls

Brain Region		Hemisphere	t	P	MNI Coordinates (x, y, z)
Frontal	Medial orbital	Left	3.389	0.0018	-5, 54, -7
		Right	4.029	0.0003	8, 52, -7
	Superior orbital		3.954	0.0004	18, 48, -14
	Middle orbital	Right	3.611	0.0011	38, 33, 34
	Inferior triangle		3.884	0.0008	50, 30, 14
Amygdala		Right	-5.507	7.19E-06	27, 1, -18
Calcarine		Left	-6.808	9.19E-08	-7, -79, 6
Olfactory bulb			-7.763	4.97E-09	-8, 15, -11
Lingual			-9.599	6.72E-12	-15, -68, -5
Middle occipital			-7.523	5.14E-07	-32, -81, 16
Anterior cingulate		Left	3.302	0.0026	-4, 35, 14
		Right	3.835	0.0007	8, 37, 16
Hippocampus		Left	-7.571	1.52E-08	-25, -21, -10
		Right	-6.393	2.81E-07	29, -20, -10
Parahippocampal		Left	-9.711	1.68E-09	-21, -16, -21
		Right	-9.202	2.08E-09	25, -15, -20
Cuneus		Left	-7.021	1.98E-06	-6, -80, 27
		Right	-6.441	1.24E-07	14, -79, 28
Fusiform		Left	-3.931	0.0004	-31, -40, -20
		Right	-4.254	0.0002	34, -39, -20
Postcentral		Left	-6.392	7.59E-07	-42, -23, 49
Caudate		Left	-6.385	3.48E-07	-11,11, 9
		Right	-7.039	2.28E-08	15, 12, 9
Putamen		Left	-11.091	6.37E-14	-24, 4, 2
		Right	-16.144	2.11E-18	28, 5, 2
Pallidum		Left	-3.798	0.0006	-18, 0, 0
		Right	-5.130	9.76E-06	21, 0, 0
Thalamus		Left	-7.855	9.88E-10	-11, -18, 8
		Right	-7.665	1.75E-09	13, -18, 8
Heschle		Left	-3.767	0.0008	-42, -19, 10
		Right	-4.022	0.0003	46, -17, 10

Brain Region		Hemisphere	t	P	MNI Coordinates (x, y, z)
Cerebellum	Crus 1	Left	-3.41	0.0027	-35, -67, -29
		Right	-5.802	7.32E-06	38, -67, -30
	Crus 2	Right	-4.520	0.0002	33, -669, -40
	3	Left	-5.812	7.42E-07	-8, -37, -19
		Right	-5.244	5.13E-06	13, -34, -19
	4,5	Left	-11.854	3.47E-14	-14, -43, -17
		Right	-14.138	4.92E-17	18, -43, -18
	6	Left	-10.303	6.37E-11	-22, -59, -22
		Right	-14.998	1.88E-14	26, -58, -24
	7b	Left	-3.536	0.0023	-31, -60, -35
		Right	-4.793	0.0001	34, -63, -48
	8	Left	-6.234	7.99E-06	-25, -55, -48
		Right	-7.710	3.56E-07	26, -56, -49
	9	Left	-9.012	8.93E-10	-10, -49, -46
		Right	-9.471	2.13E-10	10, -49, -46
Vermis	3	---	-7.763	1.20E-09	2, -40, -11
	4,5	---	-11.424	5.09E-14	2, -52, -6
	6	---	-7.389	5.66E-09	2, -67, -15
	7	---	-6.427	1.66E-07	2, -72, -25
	8	---	-8.585	3.99E-08	2, -64, -34
	9	---	-11.762	6.14E-13	2, -55, -35

MNI, Montreal neurological institute, and hospital

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eral studies (Ecker et al., 2016; Yang, et al., 2016; Ecker et al., 2016; Kohli, 2017). However, the increased GM density at the vermis may be corroborated by the idea of hypoplasia and loss of Purkinje neurons in this region (Courchesne et al., 1988).

On the other hand, the AS group showed decreased GM density at limbic regions (hippocampus, parahippocampus, amygdala, hypothalamus, thalamus), basal ganglia (putamen, caudate, pallidum), language region (lingual, parietal), heschle, fusiform, and cerebellum compared to HC group. Significant decreased GM density in the limbic regions which plays an important role in sensory-motor gating (Koch & Bubser, 1994) could infer the weakness of AS group in inhibiting repetitive behaviors (Hollander et al., 2005). Thalamus is the gateway to the cortex, and almost all sensory information is routed to the cortex through different areas of the thalamus (Jones, 2009) and abnormal thalamus was associated with social deficits, sensory deficits, and restricted repetitive behavior (Zuo, et al., 2019). The amygdala and hippocampus are the key components of the medial temporal lobe and are involved in emotional perception and regulation (Groen, et al., 2010). In addition, abnormal morphology in striatal structures or basal ganglia was reported to be associated with restricted and repetitive behavior (Van Rooij et al., 2018). These regions are also involved in the

Table 4. Regional changes of the grey matter density in asperger syndrome compared to autistic individuals

Brain Region		Hemisphere	t	P	MNI Coordinates (x, y, z)
Frontal	Superior orbital	Right	3.184	0.0028	18, 48, -14
	Inferior triangle		3.754	0.0010	50, 30, 14
	Medial orbital		4.143	0.0002	8, 52, -7
		Left	3.531	0.0012	-5, 54, -7
Insula		Left	-3.423	0.0019	-35, 7, 3
Calcarine			-7.237	4.31E-08	-7, -79, 6
Lingual			-9.892	3.55E-12	-15, -68, -5
Middle occipital			-7.701	4.20E-07	-32, -81, 16
Post central			-6.621	3.99E-07	-42, -23, 49
Olfactory		Left	-8.269	3.62E-09	-8, 15, -11
		Right	-3.338	0.0019	10, 16, -11
Anterior cingulate		Left	3.493	0.0015	-4, 35, 14
		Right	3.947	0.0004	8, 37, 16
Hippocampus		Left	-7.656	1.32E-08	-25, -21, -10
		Right	-6.412	6.52E-07	29, -20, -10
Parahippocampal		Left	-10.531	3.24E-10	-21, -16, -21
		Right	-9.651	3.85E-10	25, -15, -20
Amygdala		Left	-3.153	0.0037	-23, -1, -17
		Right	-5.809	4.18E-06	27, 1, -18
Cuneus		Left	-6.778	1.92E-06	-6, -86, 27
		Right	-6.701	5.54E-08	14, -79, 28
Fusiform		Left	-4.658	7.99E-05	-31, -40, -20
		Right	-3.699	0.0007	34, -39, -20
Caudate		Left	-8.071	9.48E-08	-11, 11, 9
		Right	-8.804	2.89E-09	15, 12, 9
Putamen		Left	-13.031	1.45E-15	24, 4, 2
		Right	-17.091	3.54E-19	28, 5, 2
Pallidum		Left	-4.903	2.16E-05	-18, 0, 0
		Right	-8.580	1.42E-10	21, 0, 0
Thalamus		Left	-8.991	4.55E-11	-11, -18, 8
		Right	-9.274	2.52E-11	13, -18, 8

Brain Region		Hemisphere	t	P	MNI Coordinates (x, y, z)
Heschle		Left	-4.908	3.04E-05	-42, -19, 10
		Right	-5.418	4.05E-06	46, -17, 10
Cerebellum	Crus 1	Left	-3.459	0.0022	-35, -67, -29
		Right	-5.385	1.17E-05	38, -67, -30
	Crus 2	Right	-4.479	0.0002	33, -69, -40
	3	Left	-5.791	9.78E-07	-8, -37, -19
		Right	-6.047	4.19E-07	13, -34, -19
	4,5	Left	-11.844	1.76E-14	-14, -43, -17
		Right	-14.070	5.14E-17	18, -43, -18
	6	Left	-10.469	1.24E-11	-22, -59, -22
		Right	-14.999	2.83E-15	26, -58, -24
	7b	Right	-4.556	0.0002	34, -63, -48
	8	Left	-5.587	1.38E-05	-25, -55, -48
		Right	-7.322	4.41E-07	26, -56, -49
	9	Left	-9.426	3.82E-10	-10, -49, -46
		Right	-9.659	7.81E-11	10, -49, -46
Vermis	3		-6.734	5.40E-08	2, -40, -11
	4,5		-10.408	7.79E-13	2, -52, -6
	6		-8.421	2.18E-10	2, -67, -15
	7		-8.877	5.16E-10	2, -72, -25
	8		-9.814	6.08E-09	2, -64, -34
	9		-12.733	3.45E-13	2, -55, -35

MNI: Montreal Neurological Institute, and Hospital.

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modulation of habit learning, action selection and performance (Jin & Costa, 2015).

Decreased GM density at lingual regions in AS group fits well with the language deficiency in AS individuals. In addition, reduced GM density at the fusiform in AS individuals also support the deficit of this group in face processing (Rossion et al., 2003). Moreover, decreased GM density at the cerebellum and vermis, can also be a reason for the weakness of AS individuals in emotion regulation and social cognition (Van Overwalle & Mariën, 2016), eye avoidance (Laidi et al., 2017), and social and affective processing (Riva et al., 2013).

Our study represented increased GM density in AS group compared to the HC group at the medial frontal and cingulate. These regions are mainly involved in social orienting and monitoring self-related information (Mundy, 2003) which are weak in AS and ASD individuals. This contradiction between the increase in GM density and behavioral deficits could be answered by the mechanism of the dopaminergic system. The dopaminergic activity in the medial prefrontal cortex is lower in autistic individuals (Ernst, et al., 1997). Therefore, the increased GM density in this region could be a compensatory mechanism to balance the drop in dopamine activity. Moreover, at the medial prefrontal cortex, AS patients showed higher GM density than the ASD group.

Table S1. Significant structural covariance in healthy control

Regions	Type of Association		AAL Region Number	R	P
Frontal-Frontal	Intra-hemispheric	Right	4,8	0.9	6.616E-11
			4,20	0.810	1.719E-07
			8,26	0.785	7.332E-07
			10,26	0.795	4.332E-07
			26,28	0.790	5.541E-07
		Left	3,23	0.817	1.069E-07
			3,7	0.866	2.508E-09
			19,23	0.798	3.570E-07
			21,33	0.8	3.178E-07
			3,4	0.854	7.379E-09
			1,2	0.865	2.715E-09
			5,6	0.792	4.911E-07
	Inter-hemispheric	L, R	9,10	0.836	3.049E-08
			19,20	0.844	1.584E-08
			21,22	0.805	2.270E-07
			25,26	0.857	5.568E-09
		R, L	4,23	0.830	4.542E-08
			4,19	0.792	5.132E-07
Frontal-Cingulate Gyrus	Intra-hemispheric	Right	4,32	0.807	2.078E-07
			8,32	0.823	7.604E-08
			22,32	0.796	3.983E-07
			26,32	0.861	3.977E-09
		Left	3,31	0.817	1.068E-07
			7,31	0.863	3.387E-09
			25,31	0.842	1.843E-08
	Inter-hemispheric	L, R	7,32	0.805	2.357E-07
			25,32	0.807	2.09E-07
		R, L	4,31	0.808	1.965E-07
			26,31	0.806	2.154E-07
Frontal-Insula	Intra-hemispheric right		22,30	0.785	7.322E-07
Frontal-Parietal	Intra-hemispheric right		22,68	0.785	7.430E-07

Regions	Type of Association	AAL Region Number	R	P
Insula-Insula	Inter-hemispheric L, R	29,30	0.843	1.701E-08
Insula-Temporal	Intra-hemispheric left	29,81	0.813	1.374E-07
	Inter-hemispheric R, L	30,81	0.899	7.356E-011
		30,85	0.834	1.071E-08
Insula-Cingulate gyrus	Inter-hemispheric R, L	30,33	0.809	1.856E-07
Insula-Parietal	Inter-hemispheric R, L	30,65	0.803	2.571E-07
Insula-Occipital	Intra-hemispheric right	30,50	0.794	4.523E-07
Insula-Temporal	Intra-hemispheric right	30,86	0.793	4.773E-07
Cingulate gyrus-Cingulate gyrus	Inter-hemispheric L, R	31,32	0.941	7.928E-14
		33,34	0.937	1.807E-13
		35,36	0.896	1.058E-10
Cingulate gyrus-Parietal	Intra-hemispheric left	33,65	0.790	5.506E-07
Amygdala-Lingual	Inter-hemispheric L, R	41,48	0.836	2.85E-08
Amygdala-Pallidum	Inter-hemispheric L, R	41,68	0.836	2.979E-08
Lingual (Frontal)-Pallidum	Inter-hemispheric R, L	48,67	0.849	1.055E-08
		48,68	0.844	1.580E-08
Occipital-Pallidum	Intra-hemispheric right	52,68	0.826	5.948E-08
		52,66	0.818	1.014E-07
		50,68	0.791	5.430E-07
Occipital-Occipital	Intra-hemispheric right	50,54	0.789	5.878E-07
Fusiform (Temporal)-Pallidum	Inter-hemispheric R, L	56,57	0.816	1.194E-07
Pallidum-Temporal	Intra-hemispheric left	63,85	0.817	1.113E-07
		65,85	0.821	8.470E-08
Pallidum-Frontal	Intra-hemispheric left	59,69	0.829	4.776E-08
Pallidum-Pallidum	Inter-hemispheric	Intra-hemispheric left	61,67	0.834	3.359E-08
			60,61	0.853	7.841E-09
		R, L	60,67	0.821	8.521E-08
			62,65	0.821	8.51E-08
			61,68	0.804	2.494E-07
		L, R	65,68	0.789	6.060E-07
			67,68	0.927	1.380E-12
			69,70	0.836	2.983E-08

Regions	Type of Association		AAL Region Number	R	P
Central-Central	Inter-hemispheric L, R		71,72	0.960	5.833E-16
			73,74	0.880	6.416E-10
			75,76	0.858	4.958E-09
			77,78	0.894	1.410E-10
Temporal-Temporal	Intra-hemispheric left		81,85	0.787	6.515E-07
			85,89	0.815	1.254E-07
Temporal-Temporal	Intra-hemispheric left		81,85	0.787	6.515E-07
			85,89	0.815	1.254E-07
Posterior-Posterior	Intra-hemispheric	Right	94,102	0.802	2.769E-07
			98,100	0.814	1.361E-07
		Left	97,99	0.792	5.117E-07
			93,94	0.8	3.2E-07
	Inter-hemispheric	L, R	97,98	0.917	6.579E-12
			99,100	0.873	1.312E-09
			105,106	0.840	2.196E-08
			107,108	0.816	1.188E-07
		R, L	98,99	0.803	2.575E-07
			112,113	0.820	9.011E-08

ALL: Automated anatomical labelling.

This fact may imply the better performance of AS patients in social orientation and self-reflection than ASD patients (Ashwin, et al., 2007; Cauda, Geda, et al., 2011). Moreover, the medial orbitofrontal and anterior cingulum are also involved in expressing fear or anxiety (Etkin, et al., 2011), which seems to be disrupted in children with autism and Asperger syndrome (Kim, et al, 2000).

In addition to structural abnormalities in AS and ASD in this study, just as mentioned, our findings also represented a differential pattern between ASD and AS individuals which is still controversial (McAlonan et al., 2008; Via, et al, 2011).

In our study, the AS group compared to ASD showed higher GM density at the medial orbitofrontal and the anterior cingulum and lessened GM density in several brain regions, including olfactory, insula, hippocamp, hippocampal gyrus, amygdala, calcarine, cuneus, lingual, occipital, fusiform, postcentral, caudate, putamen, thalamus, heschle, and cerebellum. Interestingly, the AS group, despite less severe behavioral and cognitive performance than ASD, presented more structural alteration (Courchesne, et al., 2005). Different patterns of changes in GM density in AS group may suggest a compensatory mechanism to maintain a better level of behavioral and cognitive performance by more alteration of the brain GM structure.

The brain structural network has a complex topology that could be better studied using a structural covariance network (Romero-Garcia et al., 2017). Structural covariance analysis is an effective approach for mapping the inter-regional anatomical association (Bethlehem, et al., 2017). Evidence from brain connectivity suggests that behavior affected by ASD is subscribed by deficits in distributed brain networks rather than single regions of the brain (Cardon et al., 2017).

In this study, the regional correlations in the SCNs were mainly positive, and more correlations were observed between regions in the right hemisphere. This lateralized

Table S2. Regional structural covariance in asperger syndrome

Regions	Type of Association		AAL Region Number	R	P
Frontal-Frontal	Intra-hemispheric	Left	1,23	0.921	3.982E-07
			13,23	0.919	4.805E-07
	Inter-hemispheric	L, R	3,4	0.948	2.378E-08
			7,8	0.925	2.927E-07
			17,18	0.916	6.178E-07
			19,20	0.947	2.413E-08
			23,24	0.937	8.203E-08
		R, L	12,31	0.93	1.711E-07
Frontal-Temporal	Intra-hemispheric	Left	13,85	0.919	4.624E-07
	Inter-hemispheric	R, L	12,81	0.920	1.979E-07
Frontal-Angular	Inter-hemispheric	L, R	13,66	0.925	2.687E-07
Frontal-Cingulate Gyrus	Inter-hemispheric	L, R	23,32	0.923	3.415E-07
			25,32	0.915	6.73E-07
		R, L	26,31	0.951	1.472E-08
Cingulate Gyrus-Cingulate Gyrus	Inter-hemispheric	L, R	31,32	0.965	1.332E-09
			33,34	0.916	6.113E-07
Temporal-Temporal	Inter-hemispheric	L, R	37,38	0.930	1.686E-07
Pallidum-Pallidum	Intra-hemispheric	Right	44,62	0.950	1.692E-08
			58,60	0.931	1.556E-07
	Inter-hemispheric	R, L	58,59	0.959	4.06E-09
			60,61	0.933	1.264E-07
		L, R	59,60	0.924	3.062E-07
Pallidum-Occipital	Intra-hemispheric	Left	45,51	0.926	2.65E-07
Occipital-Pallidum	Inter-hemispheric	R, L	50,59	0.955	8.544E-09
Pallidum-Angular	Intra-hemispheric	Right	58,66	0.923	3.457E-07
Angular-Pallidum	Intra-hemispheric	Right	66,68	0.922	3.53E-07
Central-Central	Inter-hemispheric	L, R	73,74	0.962	2.33E-09

Regions	Type of Association		AAL Region Number	R	P
Posterior-Posterior	Intra-hemispheric	Left	91,93	0.922	3.762E-07
			93,101	0.957	5.650E-09
			101,103	0.948	2.191E-08
		Right	92,94	0.920	4.257E-07
			94,102	0.945	3.139E-08
			94,104	0.920	4.224E-07
			102,104	0.953	1.157E-08
	Inter-hemispheric		93,102	0.915	6.419E-07
			101,102	0.951	1.491E-08
		L, R	101,104	0.950	1.833E-08
			103,104	0.963	2.207E-09
			105,106	0.943	4.483E-08
		R, L	94,103	0.929	1.834E-07
			94,101	0.925	2.887E-07
			102,103	0.925	2.885E-07

ALL: Automated Anatomical Labelling.

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pattern of SCN has been reported in previous studies as well (Tomasi & Volkow, 2012), (Kikuchi et al., 2013; Nielsen et al., 2014).

In the healthy control group, GM density similarities were observed between frontal-insula, frontal-cingulate, and insula-cingulate verified by previous studies (Soriano-Mas et al., 2013; Taylor, et al., 2009). Our findings emphasize the idea that functionally related regions are structurally associated (Damoiseaux & Greicius, 2009; Nair et al., 2014; Sui, etal., 2014). For instance, a correlation between GM densities at the insula and temporal region or amygdala and parietal region might be due to high functional connectivity between these regions (Paulus, et al., 2005; Bonda, et al., 1996). The correlations observed between GM densities at the amygdala and lingual region nicely fit with former studies relating the amygdala to language ability in normally developing children (Ortiz-Mantilla, et al., 2010). Interestingly, the GM density similarities were observed between more spatially local regions (inter-lobar). This finding may indicate that closed regions have associative activities in the brain (Allen, et al., 2002; Alexander-Bloch et al., 2012; Eyler et al., 2011; He, Chen, & Evans, 2007). Inter-regional structural covariance reflects the synchronism of their developmental changes, which may be related to the formation and reconstruction of axon connections during development and is regulated by intrinsic nutrition, neurodevelopmental factors, and genetic factors (Duan et al., 2020). Moreover, hyper-synchronous developmental coordination and maturation between these regions might be linked to the disruption of functional segregation and segregated network properties such as clustering and modularity (Chen, et al., 2008; Alexander- Bloch et al., 2013).

In contrast, the distant regions' similarities, for example, similarities at the occipital insula could reveal the brain integration network (Vértes et al., 2012).

In the Asperger syndrome group, fewer regional GM similarities were observed compared to ASD and HC groups. Decreased level of anatomical similarities between brain regions in AS group might be the compensatory mechanism (Butz, et al., 2009) to maintain a desired level of activity (Rudie et al., 2013), by using functional plasticity and altering synaptic strength.

In the ASD group, our findings showed regional over-anatomical similarities, compared to HC group that has been reported in numerous studies (Assaf et al., 2010;

Table S3. Significant structural covariance in Autism spectrum disorder

Regions	Type of Association		AAL Region Number	R	P
Frontal-Frontal	Intra-hemispheric	Left	3,7	0.912	8.850E-11
			5,15	0.822	2.458E-07
			9,25	0.806	6.502E-07
			13,15	0.819	3.006E-07
			19,69	0.805	6.785E-07
			23,25	0.852	3.24E-08
		Right	4,24	0.836	1.038E-07
			4,26	0.815	3.959E-07
			6,26	0.836	9.959E-08
			8,16	0.883	2.156E-09
			8,10	0.862	1.477E-08
			10,16	0.830	1.557E-07
			10,26	0.820	2.823E-07
			24,26	0.832	1.341E-07
	Inter-hemispheric	R, L	4,19	0.841	7.144E-08
			4,23	0.823	1.313E-07
			5,26	0.820	2.881E-07
		L, R	19,20	0.893	8.295E-10
			23,24	0.866	1.035E-08
			23,26	0.844	5.757E-08
			25,26	0.904	2.412E-10
			27,28	0.871	7.05E-09
Frontal-Pallidum	Inter-hemispheric	R, L	2,59	0.841	7.406E-08
			28,67	0.815	3.945E-07
	Intra-hemispheric	Left	19,67	0.864	1.282E-08
Frontal-Insula	Intra-hemispheric	Right	2,30	0.813	4.394E-07
			16,30	0.809	6.344E-07
			26,30	0.809	5.401E-07
Frontal-Cingulate Gyrus-Anterior	Inter-hemispheric	R, R	4,32	0.837	9.363E-08
Frontal-Pre Cuneus	Inter-hemispheric	R, L	4,67	0.821	2.724E-07
Frontal-Temporal	Inter-hemispheric	R, L	16,85	0.801	8.743E-07
		L, R	17,82	0.812	4.655E-07

Regions	Type of Association		AAL Region Number	R	P
Frontal-Occipital	Inter-hemispheric	L, R	19,50	0.803	7.892E-07
Frontal-Cingulate Gyrus-Anterior	Inter-hemispheric	L, R	23,32	0.84	7.967E-08
		R, L	26,31	0.880	2.985E-09
	Intra-hemispheric	Left	23,31	0.831	1.446E-07
		Right	26,32	0.912	8.303E-11
Insula-Insula	Inter-hemispheric	L, R	29,30	0.928	7.561E-12
Insula-Temporal	Intra-hemispheric	Left	29,85	0.9	3.579E-10
			29,89	0.826	1.922E-07
		Right	30,86	0.837	9.8E-08
			30,82	0.814	4.209E-07
	Inter-hemispheric	L, R	29,86	0.808	5.968E-07
			29,82	0.808	5.677E-07
		R, L	30,85	0.935	2.567E-12
			30,89	0.840	7.695E-08
Insula-Pallidum	Intra-hemispheric	Left	29,59	0.835	1.097E-07
		Right	30,62	0.822	2.515E-07
	Inter-hemispheric	L, R	29,58	0.810	5.187E-07
		R, L	30,59	0.835	1.108E-07
Insula-Cingulate Gyrus-Anterior	Intra-hemispheric	Left	29,31	0.812	4.587E-07
		Right	30,32	0.818	3.212E-07
	Inter-hemispheric	L, R	29,32	0.811	4.891E-07
		R, L	30,31	0.836	1.54E-07
Insula-Fusiform (Temporal)	Inter-hemispheric	L, R	29,56	0.805	6.763E-07
Insula-Frontal	Intra-hemispheric	Right	30,26	0.809	5.461E-07
			30,16	0.806	6.344E-07
Cingulate Gyrus-Cingulate Gyrus	Intra-hemispheric	Left	31,33	0.825	2.084E-07
	Inter-hemispheric	L, R	33,34	0.882	2.436E-09
			35,36	0.840	7.961E-08
Cingulate Gyrus-Pallidum	Intra-hemispheric	Right	32,62	0.819	2.989E-07
			34,62	0.830	1.499E-07
		Left	33,59	0.862	1.414E-08
			33,67	0.847	4.798E-08
	Inter-hemispheric	L, R	33,58	0.840	7.999E-08
			33,62	0.826	1.924E-07
Lingual (Frontal)-Pallidum	Inter-hemispheric	R, L	48,67	0.803	7.511E-07

Regions	Type of Association		AAL Region Number	R	P
Occipital-Pallidum	Inter-hemispheric	R, L	50,65	0.821	2.691E-07
			50,59	0.821	2.769E-07
Fusiform (Temporal)-Pallidum	Inter-hemispheric	R, L	56,57	0.809	5.549E-07
Pallidum-Pallidum	Inter-hemispheric	R, L	58,59	0.931	5.078E-12
			58,61	0.833	1.275E-07
			58,67	0.831	1.427E-07
			62,65	0.868	9.147E-09
		L, R	65,68	0.821	2.704E-07
	Intra-hemispheric	Right	58,62	0.816	3.629E-07
		Left	59,61	0.833	1.226E-07
			59,67	0.820	2.924E-07
Pallidum-Temporal	Intra-hemispheric	Left	59,85	0.849	4.189E-08
Central-Central	Inter-hemispheric	L, R	73,74	0.922	2.135E-11
			77,78	0.835	1.111E-07
Temporal-Temporal	Inter-hemispheric	L, R	81,82	0.832	1.362E-07
			85,86	0.867	9.626E-09
	Intra-hemispheric	Right	84,88	0.878	3.470E-09
		Left	85,89	0.888	1.354E-09
Posterior-Posterior	Inter-hemispheric	L, R	91,92	0.840	7.8E-08
			97,98	0.906	1.8E-10
			97,100	0.869	8E-09
			97,110	0.868	8.732E-09
			99,100	0.854	2.775E-08
			101,104	0.830	1.499E-07
			103,104	0.866	1.05E-08
			105,106	0.896	5.953E-10
			111,112	0.864	1.234E-08
	Inter-hemispheric	R, L	110,111	0.837	9.715E-08
	Intra-hemispheric	Left	95,97	0.810	5.268E-07
			97,99	0.851	3.447E-08
			101,103	0.873	5.596E-09
		Right	96,110	0.882	2.518E-09
			98,110	0.865	1.098E-08
			98,100	0.856	2.356E-08

ALL: Automated anatomical labelling

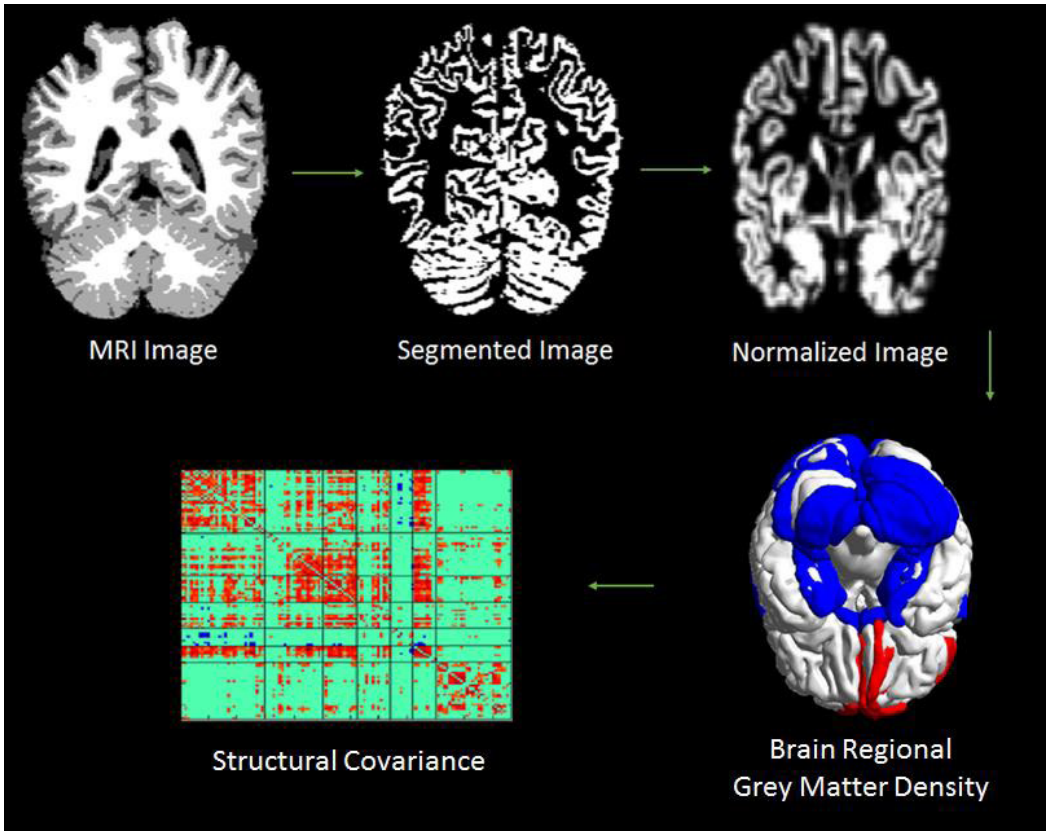

Figure 1. Processing pipeline

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Kana, et al., 2011; (Rudie et al., 2013; Kennedy & Courchesne, 2008; Nair et al., 2014; Rudie et al., 2011; Dickstein et al., 2013; Kennedy & Courchesne, 2008). Local overconnectivity (GM density similarities) in SCN of ASD individuals were mainly observed at the frontal and posterior fossa in our study which has been reported in previous studies (Courchesne & Pierce, 2005; Keown et al., 2013; Sahyoun, et al. 2010). A distal pattern of occipitofrontal functional connectivity is related to the symptom severity of ASD (Jao Keehn et al., 2019). Previous studies suggested excessive connectivity within the frontal lobe, whereas connectivity between the frontal cortex and other systems is poorly synchronized in ASD, which may reflect impairment of the fundamental frontal function of integrating information from widespread and diverse systems (Courchesne et al., 2007).

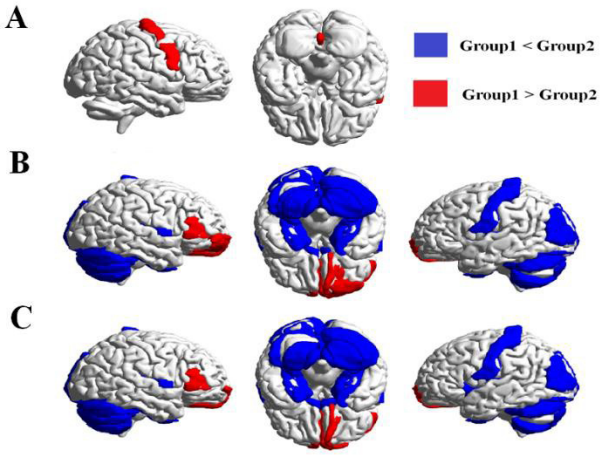

Figure 2. Significant differences of the brain regional grey matter Density between the groups

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A) Autistic and Healthy controls; B) Asperger syndrome and Healthy controls; C) Asperger syndrome and Autistic.

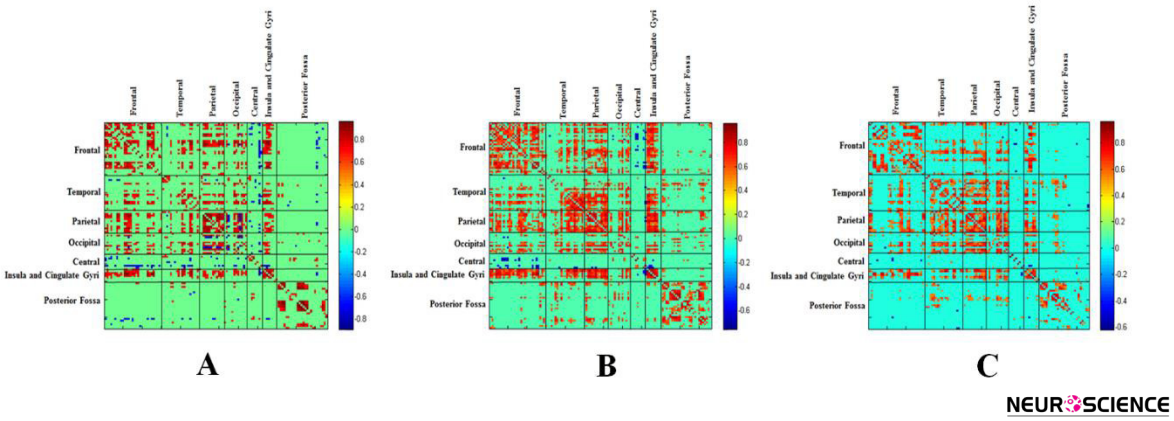

Figure 3. Structural covariance network in asperger (A), Autism spectrum disorder (B), and healthy controls (C)

Overconnectivity in SCN of ASD was also observed between the insula and cingulate regions. Local overconnectivity at the frontal regions in ASD can be taken as attenuation of cortical differentiation in frontal regions in ASD individuals by enlargement of frontal regions (Sadeghi et al., 2017a) and reducing the mini-columns (Buxhoeveden et al., 2006) and widening them (McKavanagh, et al., 2015; Vissers, Cohen, & Geurts, 2012). The GM density at the insula showed increased similarities with other brain regions in ASDs. Insula is part of the salience network (Nelson et al., 2010) that is involved in many cognitive functions, including subjective feelings (Ebisch et al., 2011), processing vestibular/auditory information (Cauda, D'agata, et al., 2011), emotions (Seminowicz & Davis, 2006), language and mood stability (Flynn, 1999). Because ASD individuals are weak at the above-mentioned functions, we think that attenuation of the insula's anatomical links with other parts of the brain leads to less efficient function (Vissers et al., 2012). A similar hypothesis may be applied to our findings in cingulate gyrus that mainly involves the understanding of other's emotional experiences (Saarela et al., 2006), emotional salience monitoring, general environmental monitoring, response selection, and body orientation (Taylor et al., 2009) that could be linked to repetitive and restricted behavior in autism (Vissers et al., 2012).

5. Conclusions

This study shows the potential of using a pattern of regional grey matter density to differentiate various ASD subtypes. Our findings also indicate the structural covariance network could be used for the discrimination of AS from ASD and HC groups. Less regional GM density together with fewer similar regions in terms of GM density in AS group may suggest a compensatory mechanism to overcome the behavioral dysfunctions in autism. The attenuated structural differentiation could be a reason for less efficient information segregation and integration which lead to cognitive dysfunctions in autism. Our findings provide another insight into understanding the pathology of autism and we hope to be used for intervention purposes.

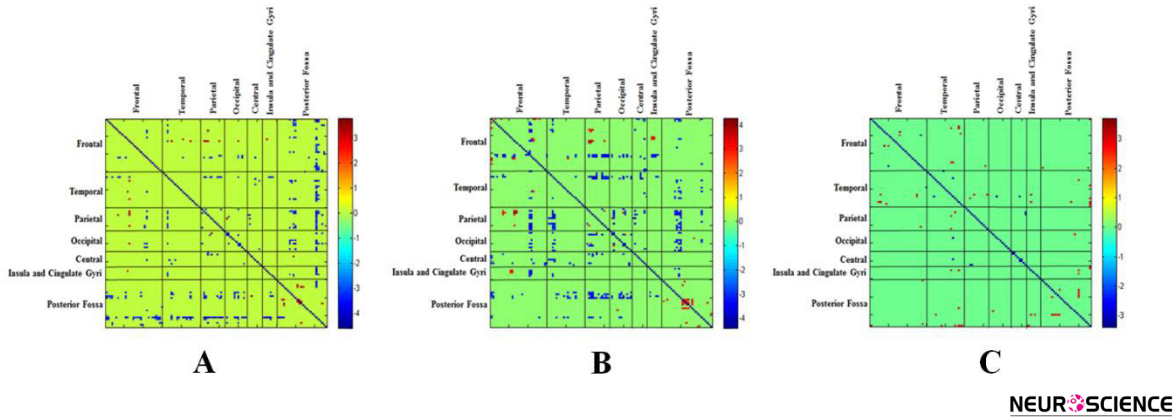

Figure 4. Differential pattern of structural covariance network between asperger and autistics (A), asperger and healthy controls (B), and autistics and healthy controls (C)

Study limitation and strength

This study has some limitations. The study was limited to male subjects, and the number of participants varied in each group. Therefore, caution should be emphasized against generalizing the results across different age and gender groups, and the severity of the disease should be considered as well. It should be noted that we only investigated the alteration of the regional GM density and their inter-regional covariations in this study. For sure, using other imaging modalities such as diffusion tensor imaging could improve our understanding of the SCNs by a direct assessment of the structural connectivity.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles are considered in this article. The participants were informed of the purpose of the research and its implementation stages. They were also assured about the confidentiality of their information and were free to leave the study whenever they wished and if desired, the research results would be available to them. A written consent has obtained from the subjects. Principles of the Helsinki convention was also observed.

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Authors' contributions

Conceptualization and supervision: Reza Khosrowabadi; Methodology: Afrooz Seyedebrahimi; Investigating and writing-original draft: Farnaz Faridi; Review and edit: All authors; Data collection and analysis: Afrooz Seyedebrahimi and Reza Khosrowabadi.

Conflict of interest

The authors declare no conflict of interest.

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